Causal Explanations in an Expert System For Diagnosis

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My thanks to Dr. Eugene Eisenberg, without whose time, patience and generosity, this project could never have been completed.

1.0 Introduction

The practice of medicine is an inherently knowledge-intensive process. With the passing of every year, clinical decision-making becomes increasingly more complex. New information is continuously added to the already overwhelming body of medical knowledge. To help clinicians cope with the complexity and volume of the information in medicine, researchers in the field of medical informatics have been developing medical expert systems for computer-assisted decision support.

In recent years there has been an effort to incorporate causal knowledge into the expert system knowledge bases (Patil 1986; Patil, Szolovits & Schwartz, 1981; Swartout 1983: Wallis & Shortliffe 1982) Experts with a causal understanding of a biological or physical system, can reason about faulty systems when they present atypically or in unfamiliar situations. Causal knowledge is used to make predictions about the behavior of a system and supplants heuristic reasoning when that cannot be applied. Pathophysiological knowledge is causal knowledge of normal functioning and structure of the human body, and how disruption to either of these results in disease. Physicians use causal reasoning to diagnose disease, predict outcomes and to communicate their understanding of

a problem to other physicians.

Current diagnostic expert systems are generally rule-based. Rules are used to capture heuristics or "rules of thumb" in the form of IF-THEN rules. By combining the rules or knowledge base with an inference engine, it is possible for these systems to generate and test hypotheses.

Traditionally, the explanation capabilities of rule-based expert systems have been derived from the decision traces produced by the program during consultation. This allows the program to explain its reasoning, by showing which rules were satisfied in order to draw a conclusion. However, this technique has not allowed the program to provide explanation of the underlying causal model. If expert systems are to truly support expert level performance and to provide an understandable interface with users, then they must be able to represent and explain the causal knowledge of a domain.

In this paper we develop a knowledge representation for a pathophysiological model of endocrine disorders in the thyroid. Causal knowledge is represented at different levels of detail or what we refer to as conceptual points of view(Miyake 1986). This type of organization provides a

strategem for producing explanations at the appropriate level of detail.

Using the methodology of Kuipers and Kassirer (1984), we developed a causal model that reflects both the empirical knowledge of an expert and the scientific knowledge from the domain. It involved collecting and analyzing observations of an expert solving clinical problems, explaining pathologies and incorporting knowledge of the domain derived from medical textbooks.

The paper is organized as following. We review the pertinent research including a brief review of explanation capabilities in medical expert systems and the representation of causal knowledge on multiple levels. Next, we summarize the basic physiology of the thyroid. This leads us to generalize a conceptual model of negative feedback and a multileveled hierarchy. We do this with the common example of a furnace and thermostat model. An outline of the methodology follows that. Finally, we in turn show our results and discuss them in relation to the multileveled model of feedback that we developed earlier.

2.Ø Related Research

This paper addresses two important research interests in

the area of explanation capabilities development and knowledge representation:

1. How to represent knowledge at varying levels of detail so that explanations may be presented according to the most appropriate level.

2. How to represent deeper pathophysiological knowledge, so that it can be intergrated into knowledge bases and used to justify and explain some of the more compiled knowledge used in problem solving.

2.1 A Brief Review of Explanation in Medical Expert Systems.

Explanation capabilities are important for expert systems to have. Explanation serves to justify conclusions, make apparent the reasoning of the program, and educate users in areas they are unfamiliar (Shortliffe 1984). In a survey of physicians, the most desired ability of an expert system, was to provide explanation (Teach & Shortliffe 1984). Causal explanations include imparting a mechanistic understanding of what has gone wrong in a patient and how that manifests itself in a particular patient.

MYCIN (Shortliffe 1976), one of the first medical expert

systems, has the ability to explain how its conclusions are reached based on the program trace that is generated during consultation. The program trace consists of all the rules whose conditions were satisfied either by an answer given from the user or from a conclusion drawn by another rule. The rules themselves encode clinical heuristics or rules of thumb which are known to be effective. The program can be requested to show why a proven conclusion is true or to give the purpose for asking a question of the user. If the user wishes to know why a conclusion is true MYCIN displays all the supporting evidence (antecedents) for the conclusion in that rule.

Mycin can display the rules and antecedents which lead to a conclusion. The rules, however, are often a highly compiled form of knowledge themselves and therefore may not satisfy the user's need to **understand** how the antecedents actually support the conclusion. The implicit pathophysiological basis for them is not included in the program. Swartout (1981) characterized this state of affairs with a good analogy:

> "The information needed to justify the program is the information that was used by the progammer to write the program, but it does not have to be incorporated into the program to perform successfully--just as one can successfully bake a cake without knowing why baking powder appears in a recipe."

To overcome this, Swartout directly encoded pathophysiological knowledge into the knowledge base. The program generates the domain code that actually performs the diagnosis, using an automatic programmer. The implemented program, DXPLAIN, is capable of both answering requests of the same nature as MYCIN, but in addition it is able to use the deeper encoded knowledge to generate explanations. The user is told why the question or answer was appropriate in the larger context of the patient and pathophysiological knowledge. However, there is no attention given to the level of detail of the produced responses.

2.2 Representing Complex Knowledge at Different Levels of Detail:

Work in causal networks by Patil et al. (1981) formed a basis from which causal explanations are generated. ABEL (for Acid-Base ELectrolyte program) which is the program they designed, has encoded in its knowledge base pathophysiological knowledge at different levels of detail. This allows the program to generate robust explanations for the patient manifestations.

Wallis and Shortliffe (1982) have done some related research in this area. In an attempt to generate "tailored

explanations" they assign values to rules. Each of the rules or links in a causal chain has two associated values, one for complexity and one for importance. This allows algorithms to be implemented that can manipulate the individual links according to their comlexity or level of detail and determine when they should be included in the explanation. However, this was never realized in a program.

Both Wallis, Shortliffe (1982) and Patil et al. (1981) make progress in terms of being able to master the computational constraints necessary to represent a multilevel causal model. However, the process that determines which level a given object is placed in the structure is largely ad hoc. In the case of the complexity and importance values, these are integer values between one and ten chosen by either the programmer or the expert. What is lacking are empirical constraints upon the knowledge representation, which are derived from the structure of an expert's model of that domain. It is this missing component, that this paper addresses: determining the structure of the expert's pathophysiological knowledge and using that to guide the explanation, both in content and in level of detail.

2.3 Causal Models and Knowledge Representation:

Causal models and their representation play a central role

in this project. We next briefly describe causal networks in relation to their representation.

A physical system can be described in terms of its attributes or parameters. The state of the system can be captured by the set of values of its attributes at a given time-point. Biological systems display homeostasis or the ability to maintain certain parameters within a certain range, even though enviromental or other forces sometimes act to change them.

Qualitative reasoning about physical models generally involves determining the behavior of a system from the correct representation of its structure. The structure itself is decomposable into individual components, each with structure and behavior of its own. The behavior of the system as a whole is determined by the connections between the components.

Most qualitative models use constraint propagation(Bobrow 1985). This is a representation in which the system's parameters are constrained in defined ways in relation to one another. Perturbances to a given parameter can be propagated through the constraints of the network changing the values of the other linked parameters. A qualitative

model replaces quantitative values of the parameters with qualitative ones, ie. high, low, increasing or steady.

Causal networks can be used to describe chains of causal events of the type: a caused b which caused c, etc.. With propagated constraints, the initial event is a change of some continuous variable-a which constrains the possible states or values of a second continuous variable-b. The first event (change in state a) may be thought of (logically) as causing the second event (change in state b), even though in actuality both events occur simulataneously.

The structural relationships and simulated behavior of causal models can be implemented in computer programs. Kuipers & Kassirer (1984) developed a program for describing the behavior of a mechanism underlying edema, which often occurs in a condition called the nephrotic syndrome. Edema is the movement of fluid from the blood to the interstitial tissues across the capillary walls.

With the methods they developed, Kuipers & Kassirer utilized three separate sources of information to identify the content and structure of the knowledge representation and to develop the subsequent computer program. The first

source was from the detailed analysis of transcripts of experts solving problems. Physicians were asked to explain how the protein loss from the blood (in the nephrotic syndrome) caused edema. Verbatim transcripts were taken and analyzed. The analysis provided imformation about the depth of detail in the expert's model and the actual relevant knowledge needed by an expert to solve the problem. Numerical values for the parameters involved in edema formation are not available to the physician. If the values were readily known, edema due to decreased protein oncotic pressure or increased plasma hydrostatic pressure could easily be predicted with an equation. Yet, physicians were able to make useful predictions or hypotheses given only partial and qualitative information.

The second source of information was from what Kuipers & Kassirer call the domain model, which is the scientific theory relating to the mechanisms involved in the causal model. The domain model served to make explicit knowledge which is actually needed in problem solving but not stated in the experts explanation. This type of knowledge is found in textbooks or the scientific literature. The domain or scientific model in the instance of edema is called

Starling's equilibrium, which can be expressed as the equation:

$$\text{Fluid movement} = k[(Pc + i)-(Pi + p)]$$

where

Pc = capillary hydrostatic pressure
Pi = interstitial fluid hydrostatic pressure
p = plasma protein oncotic pressure
i = interstitial protein oncotic pressure
k = filtration constant for the capillary membrane

The last source, was derived from the computational constraints of implementing the knowledge representation in a computer program that would correctly simulate the behavior of edema formation. All together, these three sources provided the necessary information to characterize the content and structure of the domain knowledge.

In the representation scheme used by Kuipers(1984) continuous parameters are each assigned two types of values, an ordinal value and a IQ value (incremental qualitative value). Each of the variables in Starling's equation were represented by one of these parameters. The relations between these parameters were represented by constraints. The constraints consist precisely of a set of parameters and a set of axioms stating the relationship between the values of two or more parameters. There are five types of constraints: addition, multiplication, functional relationship, derivative, inequality and

conditional.

The structural description results from linking the individual constraints through commonly shared parameters, which represent the continuous variables of interest. The simulation of the behavior is begun by initializing the ordinal and IQ values. This is followed by the propagation cycle, which is the propagation of these parameter values through the constraints until all the parameters have both an IQ and an ordinal value. This indicates the end of the first qualitative state and now prediction rules are applied to predict the ordinal values of the next qualitative state. The propagation/prediction cycles continue until the system reaches a steady state.

Kuipers and Kassirer (1984) implemented the structural description of edema formation they derived from analysis of the protocols and from the domain knowledge using the program ENV. The simualtion correctly described the behavior of edema formation based on the explanation given by an expert. Thus, they have established a methodology for determining the structure and content of a physician's causal model. In the next section we introduce the domain of thyroid physiology.

3.Ø Endocrine Physiology of the Thyroid:

The thyroid belongs to a group of organs, named the endocrine system which is responsible for the control and overall integration of the other body organ systems (see Figure 3-1). The thyroid is primarily involved in the regulation of body metabolism. Through release of thyroid hormone, the thyroid is able to modulate the rate of metabolism of the cellular machinery.

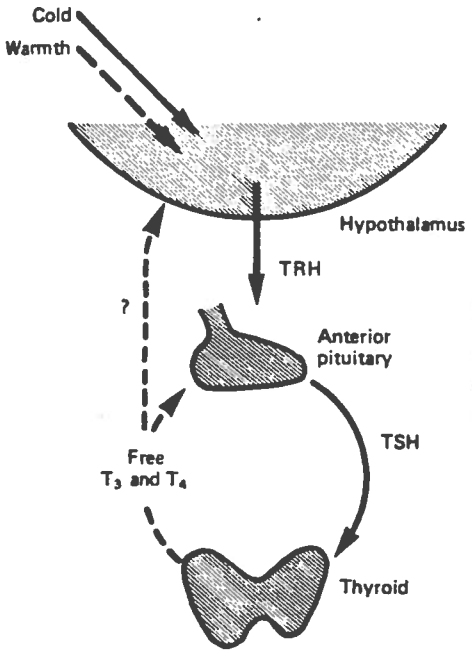

Figure 3-1. Physiological control of thyroid secretion. Solid arrows signify stimulation; dashed arrows, inhibition. Taken from Review of Medical Physiology, (Ganong 1983 p.263).

The pituitary is the gland primarily responsible for the regulation of thyroid activity. It secretes Thyroid

Stimulating Hormone (TSH) which as it names implies stimulates the thyroid to release greater thyroid hormone. Thyroid hormone in turn stimulates the body tissues and the cells to burn more fuel and oxygen. The rate of this overall activity is called the Basal Metabolic Rate (BMR). Blood concentration levels of thyroid hormone control the BMR.

The concentration of thyroid hormone in the blood also controls the rate of TSH secretion by the pituitary. Of lesser influence is the concentration of TSH Releasing Factor (TRH) which is secreted by the hypothalamus. It's levels determine the "set-point" of the pituitary. When thyroid hormone levels become too high, there is increased negative feedback on the pituitary making it less responsive to the TRH released from the hypothalamus. This negative feedback stops the pituitary from releasing TSH and this diminishes thyroid hormone production and release, bringing down blood concentrations of thyroid hormone levels.

Conversely if thyroid hormone levels tend to the lower side of normal, there is less feedback on the pituitary and TSH secretion goes up. The thyroid is stimulated to begin producing more hormone and the hormone levels return to normal.

In pathological conditions, too little or too much thyroid hormone is produced. When there is too little hormone produced the condition is called hypothyroidism and when there is too much, it is called hyperthyroidism, also known as thyrotoxicosis.

There is another level of detail describing the activities of the thyroid cell, which includes trapping of iodine (to be incorporated in thyroid hormone), secretion of thyroglobulin into the colloid, and proteolysis of the colloid with subsequent release of thyroid hormone from the cell. It is not important, here, to explain exactly how these mechanisms all relate to hormone production in the thyroid cell. Though they are important to the knowledge representation. We present the cellular activities merely to illustrate more detailed descriptions of thyroid hormone production and control. We next generalize a model of negative feedback that will help to structure our representation of the thyroid and thyroid hormone regulation.

4.Ø Hormone Regulation and Control

4.1 Negative Feedback:

Much of what the body and its subsystems perform are the maintenance of important variables within a defined and narrow range, or steady state. This occurs at all levels of organization: organ system, tissues, cellular, intracellular and molecular. A common model for systems involved in maintaining steady state are negative feedback loops.

A typical pedagodical model for negative feedback is the control of temperature in a heated house. By analyzing this model at increasingly greater levels of detail, a multileveled model can be developed. In this model there is a thermostat (sensor) which measures the temperature of the house (a continuous variable) and a furnace (effector) which heats the house . When the temperature drops below the setpoint (ex. 7Ø degrees) of the thermostat, the thermostat sends a signal to the furnace to turn on. The temperature of the house is then raised until the thermostat measures a temperature above 7Ø degrees, after which the heater shuts off. This completes the description of the structure and behavior of the system at the most general level of detail; its objects and causal relations.

4.2 Multileveled Structures:

The thermostat in the previous example is actually performing two functions: it detects the temperature in the enviroment and it sends a signal to the furnace when that temperature goes below 70 degrees. At a deeper level of analysis then it has two functions, which themselves must be linked so that the thermostat sends a signal only when the temperature is below 70 degrees and never at any other time.

The thermostat seen from this perspective can be conceptualized as containing a subcomponent for sensing the temperature in the enviroment, (sensor-which can be a coil of metal) and a subcomponent for sending the electrical signal to the furnace (an effector). Between the sensor and the effector there is some form of communication that assures the proper timing of the message sending to the furnace.

Likewise, the furnace itself must have a subcomponent which senses the arrival of a signal from the thermostat (sensor) and a subcomponent which produces heat when that signal arrives (effector- often a gas flame). Again there must be communication between the sensor and the effector, in order

that the furnace is on only when the signal from the thermostat has arrived and at no other time. This completes the description of the system at a second more detailed level of complexity.

This description is simplistic but it demonstrates how deeper levels of analysis reveal new conceptual points of view in the system. Each of the conceptual points of view represent a level of detail in the model. There is vertical integration of levels. Further analysis of the above example could reveal more and more levels down to the molecular-physical changes which occur in the metal coil. As we move down levels there is increasingly greater detail. As we move up levels there is greater explanation and understanding of the system as a whole. This model of feedback is compatible and similar to one developed by Miyake (1986). She named this framework a function-mechanism hierarchy. Any mechanism can be decomposed into subfunctions. The sub-function itself can be broken down further into lower level mechanisms. this is repeated building a hierarchy.

An explanation which is at too little or too great a level of detail for a given question does not adequately answer the question. The level of detail required by an answer to

a question is necessarily determined in part by that question. The question might be thought of as directing the explainer towards the appropriate conceptual point of view by the mention of objects and relations in its phrasing.

In endocrinology, regulation of hormone levels is often explained in terms of negative feedback loops. The domain model can be described in the same terms as the furnace metaphor just given. Just as it was possible to analytically decompose the control structure of the heating system into multiple levels or conceptual points of view, it is also possible to do the same with endocrine regulation of thyroid hormone.

4.2 Aggregation:

Aggregation may occur in different situations. In the thyroid model aggregation is a result of many identical subunits (cells) performing identical actions simulataneously. This action when spread uniformly across all the subunits, results in the action being amplified. Conceptually, all subunits may be represented as a single prototypical subunit which performs some prototypical action. It appears that the object itself (thyroid) is performing the mass action when viewed on one level, whereas on the lower level the action is seen as being

performed by each of the subunits. However, this is represented as though it were being performed by a single prototypical subunit.

4.3 Refinement:

To explain refinement we will use an example from the previous furnace model. If someone wanted to know how the temperature of the house is maintained at 70 degrees, how might we explain the answer to them? A typical response might be to discuss the relation of the furnace to the thermostat and the furnace to the temperature. But, if the questioner then wants to know further how the thermostat actually measures the temperature, then we must refer to the structures within the thermostat.

Notice we began in the first question discussing objects and relations occuring in the top level and then in the second question we are forced to drop a level and describe an object occuring at the level below it. We call this refinement.

With refinement, there is the movement from a description of a complex down to a description to one of its component parts. The relation is a is-part-of relationship. This happens when it is necessary to refer to an object at a

lower level. The concepts of aggregation and refinement will be important factors in the knowledge representation.

5.Ø Methods

The methodology developed by Kuipers & Kassirer (1984) is very well suited to our needs. It not only addressed the gathering and analysis of verbal protocols from the expert but it also included how to incorporate domain knowledge from other sources other than the expert. This information is derived from the scientific model of the domain and is used to make explicit the compiled knowledge of the expert that is not revealed by analysis of their protocols.

We next present the outline of the methodological steps with a brief summary and explanation of each. We refer the reader to the Kuipers & Kassirer (1984) paper for a detailed account of the methodology.

5.1 A presentation of briefly summarized clinical problems in the typical case format to an expert:

The problems were from clinical cases in the books Endocrinology Case Studies (Mazzaferri 1971), The Thyroid Diseases (DeGroot 1984), and one problem was derived from reported findings in the Journal of Clinical Investigations. In the earlier sessions we found that the

expert discussed very little pathophysiology during the problem solving portions of the interview. For that reason, we tailored our clinical cases to be as short and concise as possible, and we emphasized the time spent in cross-examination. Cross examination followed each clinical case and included questions such as:

a) What is the etiology and pathogenesis for each diagnostic possibility?

b) How does event-a cause or lead to event-b?

c) Why is a variable elevated/normal/decreased?

d) What accounts for state-a?/How do you explain variable-a?

e) What value would you expect to see and why.

The expert is a endocrinologist in private practice. He was requested and prompted to speak out loud as he solved the cases and folowing this the cross examination took place. Four sessions were recorded and verbatim transcripts made. Two sessions (most recent) were analyzed. The interviews were approximately one half hour each. The verbatim transcripts used in the analysis are in Appendix A and B.

5.2 Analysis of transcripts:

The first phase of the analysis was to identify the basic components of the transcript. To do this we made verbatim transcripts and broke these down into small phrases. Each

phrase has a line number, with no special importance other than as a reference to where it was located in the transcript. Those portions of the transcript dealing with the pathophysiology were studied and the domain objects and relations were identified. Then the causal relationships were identified. In the second phase we preceded to identify the different levels, though the conceptual framework had been set for these from the earlier developed multileveled model. This was accomplished by noting where each structural object occured in the transcript by line number. Each level has own their unique structural objects and so these objects are indicative of the conceptual view point of the speaker. We disregarded structural objects in the following situations:

(1) When they were preceded by localizing terms, such as in, within, and on. In these situations the structural object was not the object of interest in the explanation but a physical reference to where the actual structural object being discussed was located.

(2) When they were mentioned as part of a problem case material being read out loud by the expert.

(3) When the structural object is mentioned twice in repetition, after only a short interval.

These structural objects were plotted by the order in which they appear against their defined level. Each structural object named was represented by the line number from which

it was identified from the transcript, on the graph.

5.3 The domain model is characterized:

Objects and relations were identified from the scientific literature and analyzed in a similar fashion to the transcript analysis. Prototypical diagrams are selected from textbooks to demonstrate the models and to illustrate the relationships between objects. The correspondences and differences between the transcript analysis and the domain models were noted.

Unlike Kuipers & Kassirer (1984) we will not be extracting an equation from the scientific literature. Instead, we needed to demonstrate the qualitative model that existed in the literature. This was not as easy as pointing to an equation. It should be remembered that both qualitative and quantitative sources may constrain the knowledge representation and make explicit information that was not stated in the expert's explanation.

5.4 The knowledge representation is assembled.

From the information provided in the previous sources a knowledge representation was constructed which satisfies these constraints in addition to the computational constraints. Computational constraints are the inclusion of

relationships between objects necessary for that knowledge representation structure to correctly perform the simulated behavior.

6.0 Results

6.1 Analysis of Transcript:

The analysis of the transcript revealed several objects and causal relations from the cross examination. Below are two excerpts from the verbatim transcripts. We analyze them to demonstrate how we arrive at certain conclusions. Later we categorize all the objects and their relations to one another.

Figure 6-1 Here the expert explains why a patient becomes thyrotoxic when their pituitary is not sensitive to the regular levels of T3 in their serum. The question asked is between the bars of asterisks. Numbers preceding each line indicate the postion in the verbatim transcript.

```
**********************************************************
(Q7) So how does this insensitivity cause you to be
thyrotoxic?
**********************************************************
94    Because the pituitary not sensing normal T3 level
95    puts out more TSH
96    which stimulates the thyroid
97    much the same way TSIG does.
98    there's just too much TSH produced
99    because the pituitary is not told to shut off
100   at the normal level of T3.
101   It doesn't shut off until the
102   T3 level gets excessively high.
```

The frame of the excerpt presented, (see Figure 6-1), is one of objects performing actions upon other objects, causing those objects to change state or rate of activity.

Actions are notable for there similarity to prototypical actions occuring in negative feedback control: "sensing", "puts out more","stimulates", "produced", and "shut off" are all examples of this.

6.2 Terminology- structure, parmameter and agent objects: The objects in the above excerpt can be divided into structural objects, parameter objects and agent objects. (see Figure 6-2) Structural objects correspond to discrete physical entities. They are anatomically identifiable physical objects, such as the thyroid, pituitary or they could also be a thyroid cell or a hormone receptor.

A structural object has inputs and outputs. Most often, structural objects are influenced and themselves influence continuous variables. For example, the structural object, thyroid gland, changes the blood concentration of T3 and T4 (output) in response to TSH concentration levels (input).

Since continuous variables, such as TSH and T4 interact with structural objects in much the same way functions are called with arguments, they are named parameter objects. In the above example the structural object pituitary has as input a parameter object, T3 and has as output the parameter object TSH. The excerpt also mentions an agent

object, TSIG. This is an antibody that acts like TSH in stimulating the thyroid cell to produce more hormone. (It is mentioned as an analogy in the explanation. It is actually not relevant to the actual process being explained.) Even though TSIG can occur in various concentrations in certain patients, it is not normally present at all in a healthy person. In contrast to a parameter object, which is a continuous variable, agent objects are dichotomous.

Figure 6-2
Objects and relations identified from the first example. The numbers following the objects mentioned are references to the line number in the transcript where they are located.

```
objects
     structural:   pituitary   [94,   99,   101   ("it")],
     thyroid[96]
     parameter: T3 [94, 100, 102], TSH [95]
     agent: TSIG(thyroid stimulating immunoglobulin)[97]

relations:
     input
          pituitary (T3) [94,99-100,101-102]
          thyroid (TSH) [96]
          thyroid (TSIG) [95]
     output
          pituitary (TSH) [95,98]
```

The next step is to identify the causal relationships in the excerpt. The initial event in the causal chain is the faulty sensing mechanism of the pituitary in detecting levels of T3. When the pituitary cannot "percieve" a normal level of T3 in the serum, it "causes" the pituitary to

increase its TSH output. TSH is the input to the thyroid. An increase in TSH causes the thyroid to increase its output.

6.4 Process Objects:

In the second example we see a new set of objects, as well as a few objects from the previous example (see Figure 6-3).

(Figure 6-3) The expert explains how the normal healthy pituitary senses levels of thyroid hormone.

```
71   T4 receptors on TSH producing cells
72   in the pituitary
73   .....there may T3 receptors too
74   I think there are some work which suggests that
75   it's actually the process of deidonation to T4 to T3
76   which actually affects TSH production
```

The "process of deiodination" in line 75 of Figure 6-3 named a process object. They are similar to structural objects, in that they receive input and return output. However, unlike structural objects, the input and output to a process object are materials which it transforms. Process objects are events located diffusely within a given system (such as inside a cell). The rate of production by a process object can also be influenced by other parameters.

(Figure6-4) Analysis of excerpt 2.

```
Objects:
     structural-
          T4 receptors [71]
          cell [71]
          T3 receptors [73]
          pituitary [72]
     process object-
          deiodination of T4 to T3 [75]
          TSH production [76]

Relations:
     input
          process of deiodination (T4)
          TSH production (T3)
     output
          process of deiodination (T3)
```

An example of a process is the synthesis of thyroid hormone in the thyroid cell. This process occurs through many steps within the thyroid cell. It is not strongly associated with any single structure (hence why it is not called a structural object), since many are involved. Additionally, the process is influenced by the intercellualar levels of the messenger cyclic AMP. The entire process is abstractly represented by a single process-object.

6.5 Findings from the Analysis of Transcripts:

Using the methods we described earlier 42 structural objects were identified in the transcript. Fourteen of them occured in level Ø, fifteen in level 1, one in level 2 and twelve in level 3. Figure 6-5 depicts the results of this analysis from the transcript in Appendix A and Figure 6-6

shows the results derived from Appendix B.

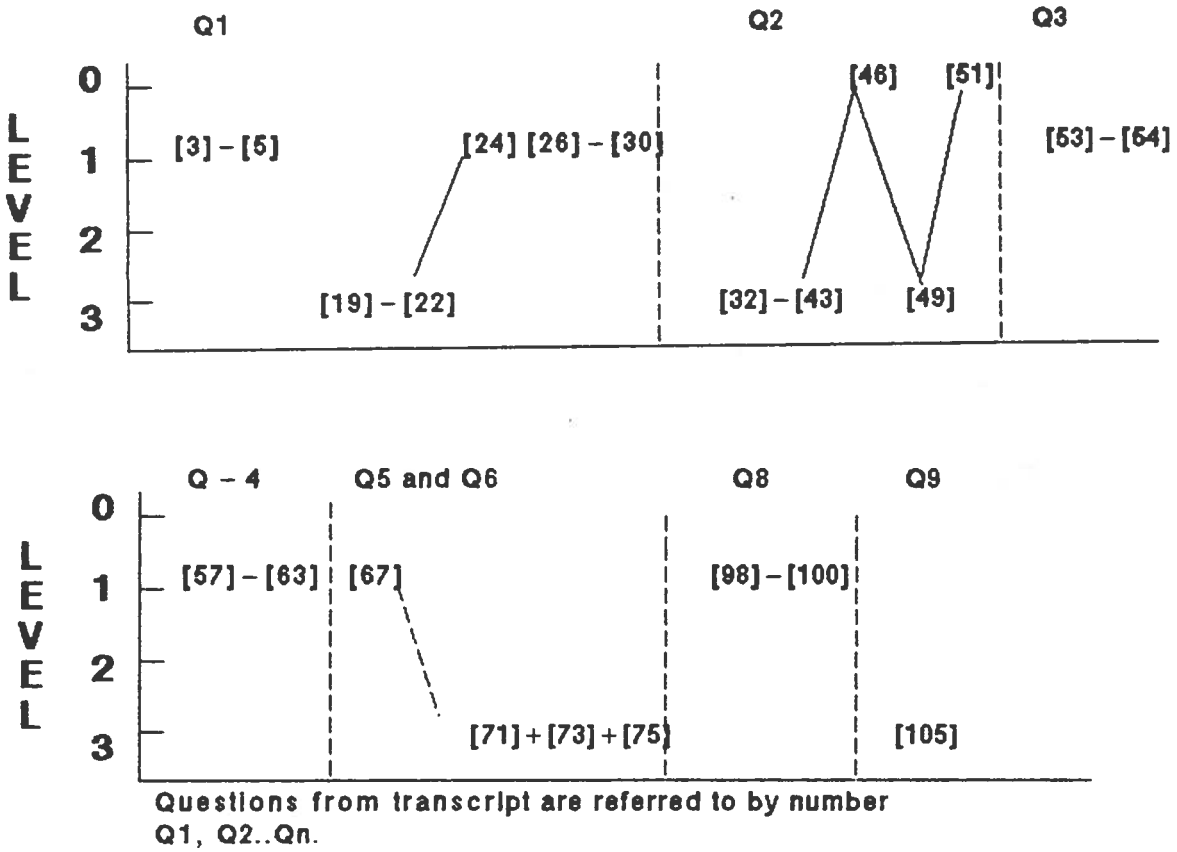

Figure 6-5. Analysis of transcript (Appendix A). Numbers in brackets refer to a structural object which is located at the corresponding line number in the transcript. Dashed vertical lines separate the responses to different questions.

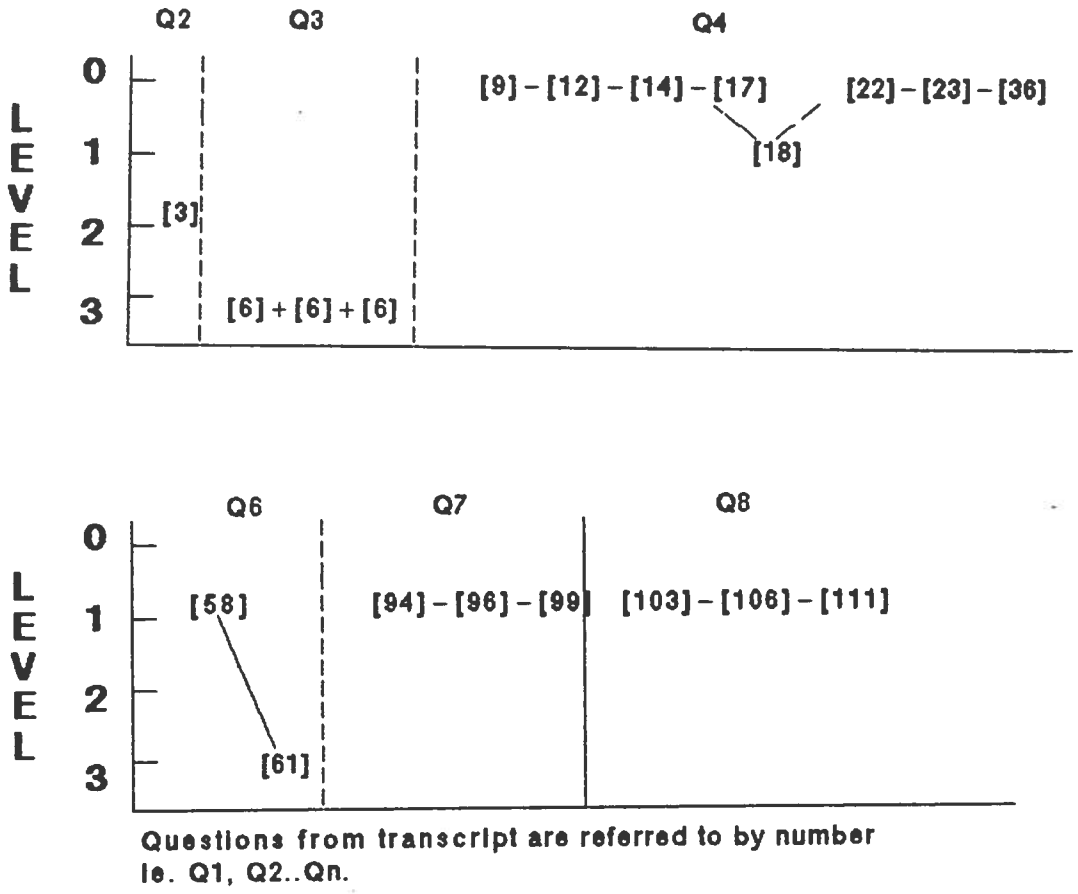

Figure 6-6. Analysis of transcript (Appendix B). Numbers in brackets refer to a structural object which is located at the corresponding line number in the transcript. Dashed vertical lines separate the responses to different questions.

(1) Conceptual Point of View:

Specific objects and relations tend to appear together in response to certain questions. There is what we believe to be a correspondance between objects mentioned and the conceptual point of view of the speaker. Perhaps not suprisingly, when the expert is asked to explain how the pituitary senses thyroid hormone levels, his conceptual point of view is directed toward certain components of the pituitary TSH cell. In the second example he mentions T4 receptors "in" the pituitary and a process of interpituitary deiodination. From this we can infer that the conceptual point of view is predominantly at the cellular level.

In contrast, in the first example (see Figure 6-2), the conceptual point of view was directed at the organ system level. The objects mentioned were the pituitary, thyroid, T3 and TSH. These are terms frequently used to discuss the thyroid in relation to other organs in the endocrine system. Common to both examples are the objects TSH and T3. These objects must then be present in both the cellular and organ system conceptual point of views. In their positions of intermediaries they might also facilitate the transition from one conceptual point of view to another, a point to which we will return to later.

(2) Localization of the conceptual point of view:

The pituitary, a structural object, as was mentioned in the second excerpt (see Figure 6-3): "... on TSH producing cells in the pituitary..". It's role here is strictly for localization and is not an object in the same sense as it was in the first excerpt (Figure 6-1). In fact it serves to orient the listener to the conceptual point of view of the discussant. There are other examples of this phenomenon. When discussing an enzyme defect that partially blocks the formation of thyroid hormone, the expert localizes his conceptual point of view for the listener:

> "..inherited enzyme defect in the thyroid in one of the steps of thyroid production..."

We do not make the strong claim here, that the word "in" and "on" are always associated with localization of a conceptual point of view. There are examples, however, where the context of the explanation does warrant the conclusion that the expert is "setting" the stage for his explanation. Sometimes the listener is perhaps left to infer the level, in the same way we are analyzing the transcripts- by noting the particular objects and relations being discussed. This means that objects of the same conceptual point of view will have a general temporal proximity to one another, a feature we utilize in analyzing

the place and order in which they appear in the transcript. We found three instances of localization occuring in the two transcripts.

An associated phenomenon is the directed localization to a particular conceptual point of view by the discussant when agent objects appeared in the discussion. For example, an agent object such as an antibody can stimulate the thyroid gland (as in graves disease). But the antibody can be thought of as being able to act on objects occuring at all levels: the antibody can stimulate the thyroid (organ level object), it can stimulate thyroid cells (cell level), or it can stimulate the TSH receptor (subcellular level). This is not three different antibodies, but the same one acting as an agent-object at three different conceptual points of view. The transcripts show this:

> "..formation of thyroid antibodies that continue to attack the gland..."
>
> "..constant inflammatory reaction relative to the antibody reaction with components of the thyroid cell..".

The explainer, therefore, chooses the level(s) at which a the actions of a particular agent are viewed. Agents can even function on the level of the person. If a normal patient (object) is given a antithyroid drug (agent-object) they become hypothyroid (change in metabolic state). Some

agent objects might have particular levels at which they are most often discussed. For instance, the enzyme defect mentioned earlier, may be thought of as an agent-object. It is perhaps, most relevantly discused at the subcellular level where it demonstrates the disruption to hormone synthesis. However, it could have as well been framed in terms of a gland, with impaired function due to an enzyme defect and unable to produce sufficient hormone (organ system level).

(3) Aggregation and Refinement:

There is one last point to make about the conceptual point of view and analysis of transcripts. Earlier we alluded to movement between levels and conceptual point of view, and the potential faciliatory role of objects which are present in more than one conceptual point of view. These movements between levels can occur for different reasons, sometimes in response to a single question.

One reason for a change in conceptual point of view, might be to move from a detailed mechanistic account of a process occuring within a subunit, to a higher level at which the result of that process across all subunits becomes apparent. This is what we referred to earlier as aggregation. An example of this:

> "...the pituitary being much more sensitive to the T3 level both in the serum and possibly due to interpituitary conversion...TSH might go up..."

The pituitary, T3 and TSH are all objects from the organ system level. The process-object "interpituitary conversion" occurs intracellularly and so belongs to the intracellular level. The rest of the explanation mostly remains at the organ system level. However in the next to last line there is an object mentioned, which is a reference to a deeper mechanism (conversion) which occurs at the intracellular level. Finally, the explanation concludes with how that particular mechanism will manifest itself on the organ system level (TSH goes up). This is therefore, an example of aggregation, since the action of decreased interpituitary conversion on the cellular level manifests itself as increased TSH on the organ level. In Figures 6-5 and 6-6, there can be seen 3 instances of aggregation, where the explanation goes from a lower level to a higher one in the course of its telling.

Another movement, moving from a higher level to a lower level we called refinement. The motivation for refinement occurs when it is desirable to explain some function in terms of its underlying mechanism (Miyake 1986). The enzyme defect which served to illustrate the process of localization is also an example of refinement. By, focusing

from the higher, more general levels down to the specific step in hormone syntesis affected, the level of detail in the explanation becomes greater. The transcript had at least three instances of this.

6.6 Categories of objects and relations as they occur within the different levels:

We have argued that levels correspond to the different conceptual point of views. They are identified from the proximity and relation of objects to one another in the transcript. The conceptual point of view is also recognized by identifying the key central structural or process object(s) in a passage which are manipulated by the various agent or parameter objects. The context of their use is also important in determining the conceptual point of view, especially since aggregation and refinement by definition involve more than one point of view. (the object can be described as similar to a "black box")

6.6.1 The Levels

The following are the descriptions of the levels as we have determined them from the transcript. They include the patient level, the organ system level, the cellular level and the intracellular level. Objects are categorized in each level. The patient level (level Ø), has one main object, the patient. The patient can be thought of as a

black box, into which input such as drugs or iodide are given and out of which come outputs such as metabolic status and lab parameters. Figure 6-7 shows these relationships graphically.

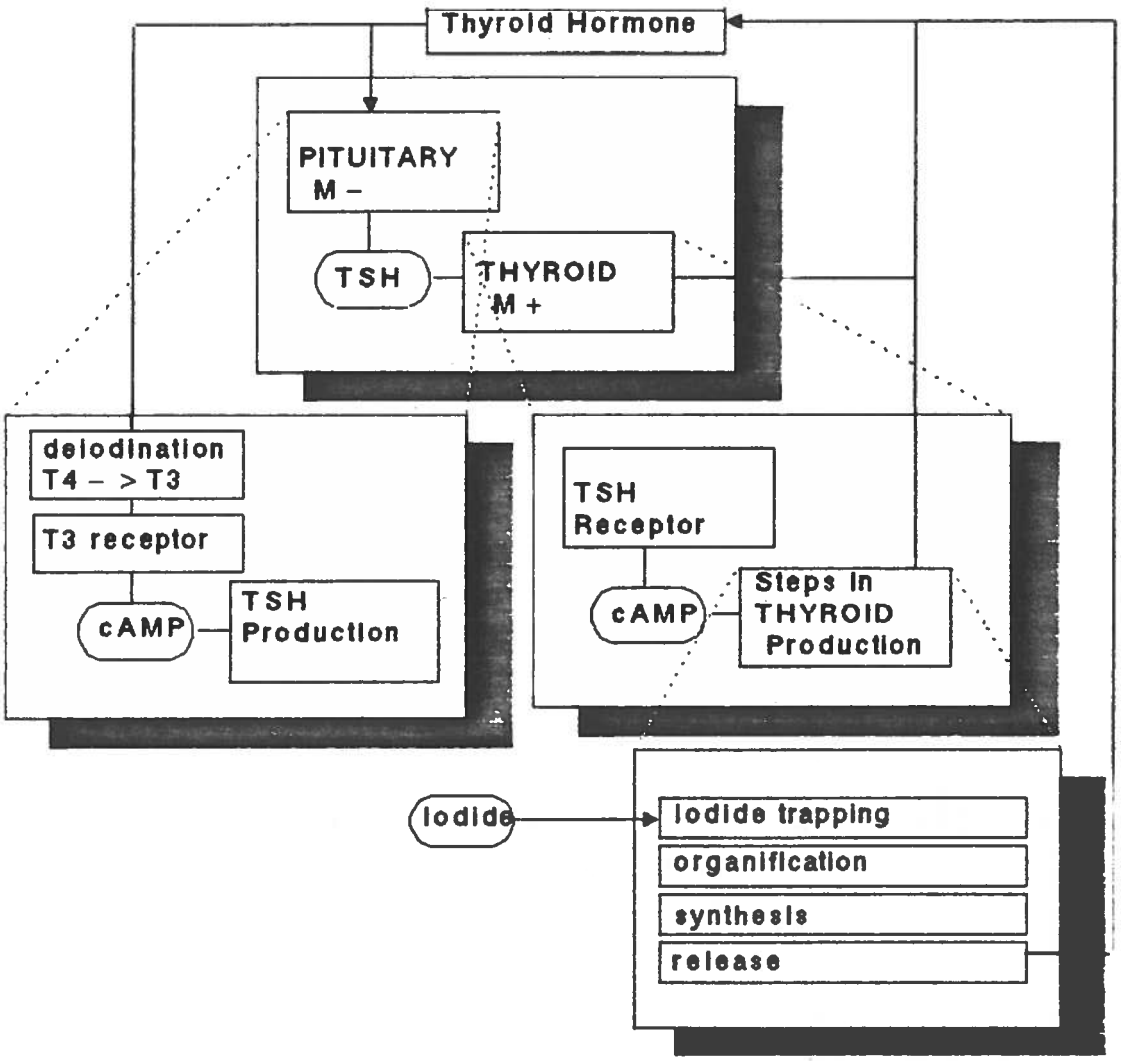

Figure 6-7. A structural description of thyroid hormone regulation. Three different levels are presented.

Level: Patient
Structural Object: patient
Agent Objects/Parameter Objects: drugs which affect thyroid function, iodide.
Metabolic status (hyperthyroid, euthyroid, hypothyroid).
Lab Parameters: T4, T3, TSH...blood concentrations

The organ system level (level 1), is a true system, with objects interacting with one another with the express purpose of regulating the blood concentrations of thyroid hormone.

Level: organ system
Structural Object: pituitary, thyroid, hypothalamus
Parameter Object: TSH, thyroid hormone, T4, T3, iodide, drugs
Process Objects: negative feedback inhibition
Agent Objects: Antibodies, drugs.

The cellular level (level 2), is similar to the patient level in that the point of view is external to that of the system. The cell is seen as a black box with various inputs and outputs. Receptors are often associated with this level, perhaps because of their frequent depiction in the literature as located on the outside surface of cells.

Level: cellular
Structural Objects: cell, antigenic components,TSH receptors, T4 receptors, T3 receptors (T4 and T3 receptors are associated with pituitary cells, but actually are located inside them. So in fact their conceptual point of view may be more appropriate to the intracellular level. However, since these

receptors are metioned as being "on" the cells in the transcript, we include them here.)

Parameter Objects: TSH, T4 , T3, iodide, drugs ...

The intracellular level (level 3), is another true system, with an emphasis on process objects, which transform raw materials into thyroid hormone or TSH molecules. It also includes the information systems which regulate the rate of these productions. The conceptual point of view here is of the internal processes and events of a prototypical cell. The sum behavior of a gland can be inferred by the behavior of this prototypical cell, when all cells are known to behave like the prototype.

Level: intracellular

Structural Object: (TSH receptors or T4/T3 receptors?)

Parameter Objects: cyclic AMP, iodide, organified iodine

Process Objects: [steps in thyroid hormone production]- iodide trapping, organification, hormone synthesis and release. T4 to T3 interpituitary conversion.

Agent Objects: iodide, enzyme defects (peroxidase deficiency)

6.7 Summary of Results

We can now summarize our findings from the analysis of the transcript: (1) Objects related to one another appear together and seem to correspond to different conceptual

point of view. We have categorized them according to level.

(2) Examples of aggregation and refinement are suggested in (three each) passages of the transcript. They probably enhance the explanatory process by facilitating the transition from one conceptual point of view to another.

(3) Orientation to a conceptual point of view takes place when the speaker refinement from a higher level to a lower one, or when the conceptual point of view is made clear by the description of structure at that level. There is also suggestion that the speaker chooses a conceptual point of view from several possible ones. This directed localization may represent the expert's preference for a particular level of detail, when explaining a particular disease process. There were three instances of directed localization.

(4) We found instances where the expert discussed the structure separately from the behavior of the model. This agrees with the findings of Kuipers & Kassirer (1984).

(5) There were a number of mechanisms discussed in the transcripts. The division of this initially

large number into several separate models with fewer objects may ease the computational demands for effectively manipulating them.

7.Ø Domain Model:

From the interview sessions we gain insight into an experts' cognitive model of a particular system: this includes both the relevant structure(s) and behavior of that system. The expert's knowledge is so compiled, however, that some of his knowledge is not brought out during the interviews. Additionally, the knowledge any given expert has is a subset of what is currently known about the particular subject and recorded in the scientific literature.

The domain or scientific model makes this compiled knowledge explicit. It also serves to show the limits of the expert's knowledge by comparison. The protocol of the expert clinician, in turn, helps to show specifically which portions of the larger body of scientific knowledge is most relevant to effective clinical diagnosis.

In the analysis of the transcript we described different conceptual point of views which we determined were present

in the transcripts. From the scientific literature we will now show many examples which support our analysis. These examples take the form of illustrations, Figures, diagrams and accompanying textual descriptions from textbooks in medicine and endocrinology. By analyzing the domain knowledge in a similar fashion as the transcripts, it is possible to show the correspondance between the domain model, the expert's model and the conceptual point of views.

7.1 Medical Textbook Description of Normal Physiology:

The prototypical diagram of the control of thyroid function is shown (see Figure 3-1). We see the structural objects of the organ system level: hypothalamus, pituitary and thyroid. Notice that each of these objects can be viewed here as black boxes or functions, with input and output. Together, the objects interact with one another, either directly or indirectly through the hormones TSH and T4. Taken as a whole these objects and their relations constitute a system. In the function-mechansim hierarchy of Miyake (1986), each structural object would be carrying out a function, and connected these functions taken together would be called a mechanism.

The conceptual point of view from the cellular level is

presented in Figure 7-2. Depicted are the intracellular events; those involved with iodine metabolism and subsequent hormone synthesis, and the regulation of these processes via cAMP and TSH. Similar to Figure 7-1 this is a collection of functions represented by structural objects (TSH receptor) and process objects (iodide transport, hormone synthesis). (Parameter objects are the TSH shown binding to its receptor and cAMP.) Therefore this too, is a system, and in Miyake's scheme a mechanism. To contrast, a functional representation at this level would be an external view of this cell. That is the cell would receive TSH as input and would have hormone as output, but there would be no explanation as to how this was accomplished internally by the cell. It would be a black box, hence a function rather than a mechanism. Once we "look" into the cell we see how the individual intercellular functions contribute separately to the production of thyroid hormone. We then can say we "see" the underlying mechanism to the thyroid cell function.

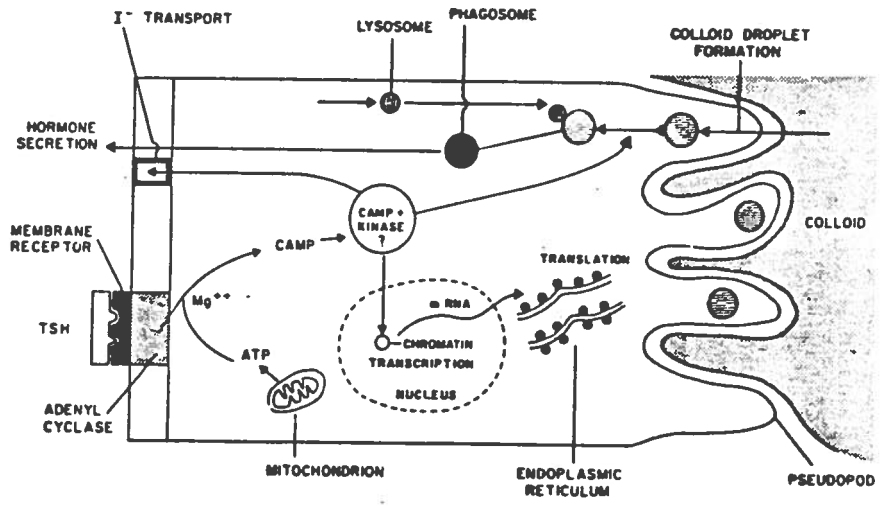

Figure 7-2. The cellular level. Intracellular events are shown inside the cell. Taken from The Thyroid Diseases (DeGroot 1984).

In the analysis of the transcript we identified a process we claim was equivalent to that of aggregation. In Figures 7-3 and 7-4, there is a demonstration of that process graphically. For example in Figure 7-3, there are the organ system level objects pituitary, hypothalamus, TSH, TRH, and T4 and T3. However, the thyroid has been replaced by what appears to be one huge cell. Indeed, its output is equivalent to the output of the entire thyroid gland and similarly its input. Aggregation is achieved here by drawing the prototypical cell, which is graphically equivalent to the entire collection of thyroid cells, which

is equivalent here to the thyroid itself.

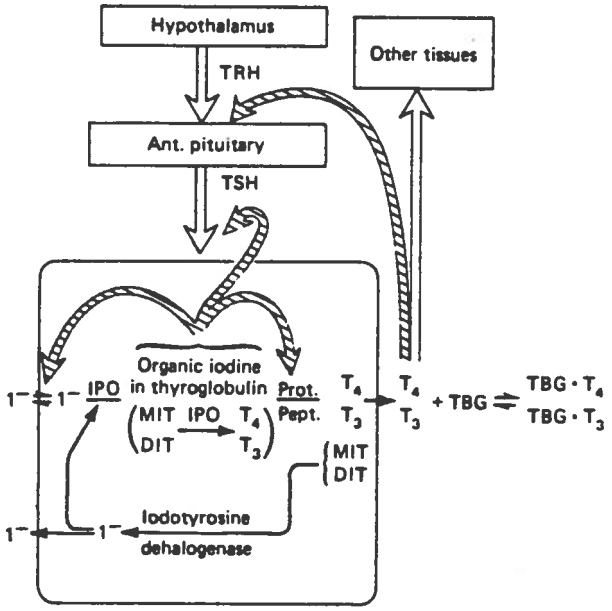

Figure 7-3. A graphical example of aggregation and refinement occuring in the thyroid. Taken from Harrison's Principles of Internal Medicine, 10th edition, (Petersdorf, Adams, Braunwald, Isselbacher, Martin, and Wilson, 1983, p 1696).

In addition, the intracellular events are depicted inside the cell. All together they represent the mechanism underlying thyroid function. Therefore, the diagram encompasses both the conceptual point of view of the organ system and conceptual point of view of the cellular level. Depending on how you look at this figure, then, it can be

either an example of aggregation or of refinement. It is an example of refinement, since it involves dropping down a level if one is interested in the underlying mechanism of the thyroid at the cellular level. On the other hand it is an example of aggregation, if you are interested in determining how a defect in one of the intracellular processes will effect the system at the higher (organ system) level.

In Figure 7-4 there is another example of aggregation and refinement, this time it involves the pituitary instead of the thyroid. Again, the organ is replaced by one large cell and there is depicted a single intracellular process, the conversion of T4 to T3 which is improtant to feedback inhibition.

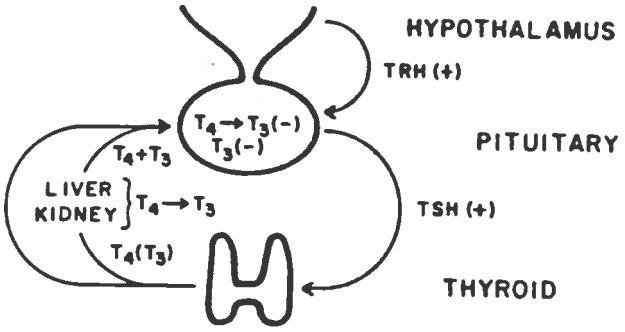

Figure 7-4. A graphical example of aggregation and refinement taking place in the pituitary. Taken from The Thyroid and its Diseases (DeGroot 1984).

From the organ system level, it should be possible to push down levels within any structural object as we have shown here with the pituitary and the thyroid. While we have not shown it, this should also be the case in principal with process objects. Parameter objects, unlike the structure or process objects, are not decomposable to other levels. Instead they seem to act similar to agent objects; appearing on different levels in accordance with the focus of the speaker's conceptual point of view. There is an upper bound to the levels at which they can appear. For instance, cAMP cannot appear at the organ system level, only at the cellular and subcellular levels.

In the Figures 7-5 and 7-6, we show some examples of a disease process at the organ system level. In Figure 7-5, TSI which is an acronym for a type of antibody is shown attacking the thyoid. Clearly, this diagram is at the organ system level. The accompanying text, which is from a textbook of medical physiology (Ganong 1983 p. 264), reads:

> "The secretion of TSH from the pituitary gland is depressed in this disease because of the negative feedback effect of the high circulating T4 and T3 levels (refers to Figure shown here). "

The next sentence from the text (Ganong 1983 p. 264) drops down a level to explain some of the underlying mechanism:

> "The cause of the thyroid stimulation is a group of antibodies against the TSH receptors in the thyroid that also have the capacity to stimulate the receptors and activate adenylate cyclase in the thyroid cells."

Notice that in pushing down a level they localize the conceptual point of view with the use of "in the <structure object>" twice. The resultant conceptual point of view is at the intracellular level. This also demonstrates how the agent object TSIG, can either act at organ system level as in the diagram or on the cellular level as described in the text.

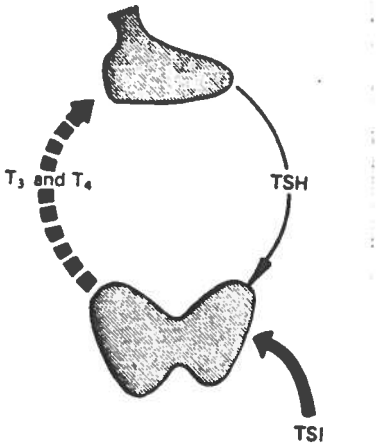

Figure 7-5. Thyroid and pituitary function in Graves disease. TSI represents an antibody which stimulates the thyroid. Taken from Review of Medical Physiology, (Ganong 1983 p.265).

Lastly, Figure 7-6 shows an organ system level view, which includes a thyroid with the attribute of a enzyme defect. Again there is aggregation, in the sense that the enzyme is located within the thyroid cells, in contrast to inside a thyroid. The output of thyroid hormone is diminished in this thyroid, resulting in increased TSH output, all phenomena at the organ system level.

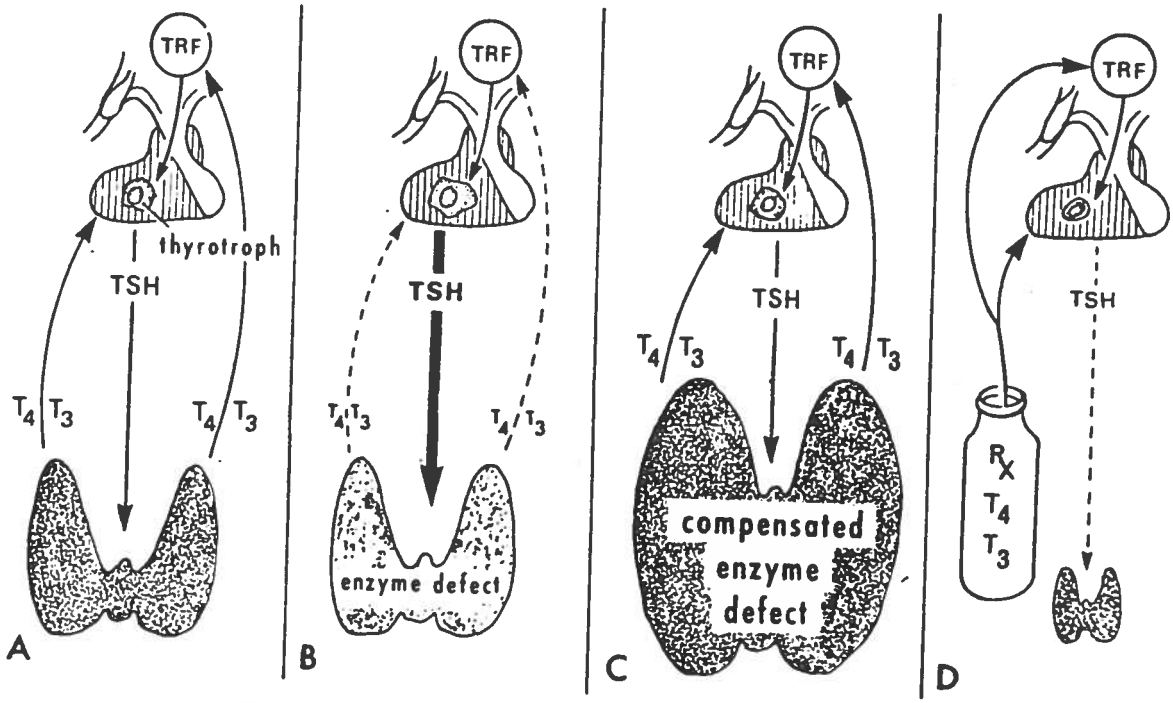

Fig. 5-3. Hypothalamic-pituitary-thyroid relationships in diffuse goiter due to enzyme defect. These figures illustrate activity of the "thyrotroph"—the cell which produces TSH or thyrotropin.

Figure 7-6. Hypothalamic-pituitary-thyroid relationships in diffuse goiter due to enzyme defect. Taken from Systematic Endocrinology (Ezrin, Godden & Volpe 1973).

From these examples we have shown how the domain knowledge is organized and descibed in a similar fashion as the expert's causal knowledge. By comparing the information present in the domain model with the objects mentioned by

the expert, we also see what information he does not use. For instance, the expert never did mention cAMP the intracellular messenger in his explanations. He also was not absolutely certain of the mechanism underlying how the pituitary senses thyroid hormone levels. Though, he did know that there were receptors for T3 and possibly T4. A couple of reasons might account this. One is that measurements of cAMP are not done routinely as a part of clinical laboratory tests, so it is a parameter that is primarily ignored by clinicians. Second, there is also no disease process associated in the thyroid with a primary failure in the formation or rate of formation of cAMP, as there is with the enzymes involved in hormone synthesis. Therefore, because it neither a measured nor a cause of dysfunction it is relatively unimportant to effective problem solving.

8.Ø Knowledge Representation

We now construct a knowledge representation based on the information we derived from the domain expert explanations and from the domain model. Figure 6-7 shows the structure of the knowledge representation for normal physiology of the thyroid and pituitary. Notice that the levels here correspond to the organ system, cellular and molecular

levels. Aggregation occurs when the function representation at level n is replaced by the mechanism from level n-1. Refinement occurs when we center attention on mechanisms and defects occuring on the level lower than the present one. Refinement is a move from level n to level n-1, and aggregation is a move from level n-1 to n.

In the simulation parameter objects have two attributes which characterize their state at any given time. The ordinal values, which are values describing qualitative amounts relative to each other: <normal, normal, >normal, and the IQ values which indicate the direction of change of that parameter: increasing, decreasing, or steady. Both values are needed to to fully characterize a parameter object at a given time point. When all parameter objects have values for both attributes, then the propagation for that qualitative state is over. The next qualitative state is started by predicting the next ordinal value of each parameter. The IQ values are propagated to complete the description of the qualitative state. Our ordinal values are normal, > normal, < normal, zero, > zero and < zero. We also define them as landmark values which are important in the prediction cycle. Landmark values are distinguished values. Parameter object values of the system gravitate towards these landmark values, during the simulation.

The constraints perform logical procedures on the ordinal values and IQ values to propagate the input of one parameter across the constraint to another parameter. In the simualtion we use an addition constraint and monotonic function constraints. Addition constraints recieve three parameters (two input and a sum). Given any two of them, the value of the third is determined using the addition constraint propagation rules. Monotonic function constraints receive two parameters; when the values of either of them are known, the other is set according to monotonic propagation rules. These rules for a monotonically increasing function are of the type M+(x)= x, while a monotonically decreasing function is M-(x)= -x (eg. x=high, -x=low).

The network alternately propagates through the constraints and then qualitatively predicts the next state. When the IQ values of all the parameter objects are steady, the system recognizes the steady state and stops the simulation.The prediction rules for predicting the next qualitative state are as follows:

(P1) If the current value of a quantity (as indicated by the IQ value) is changing in the direction of a landmark value, than move that quantity to the

landmark value.

(P2) If the parameter objects are all connected through monotonic constraints and all are changing in the direction of land mark values, then move each of them to the landmark value and set their IQ value to steady.

8.1 A simulation:

We now simulate Graves disease, a process where antibodies in the patient are directed against their own thyroid, and stimulate it in a similar fashion to TSH. This causes the person to become hyperthyroid or to have too much thyroid hormone in their blood. In figure 8-1 we show the constraint network. The circled arrows indicate the desired direction of change those parameters should move to in order to correctly simulate the behavior of Graves disease.

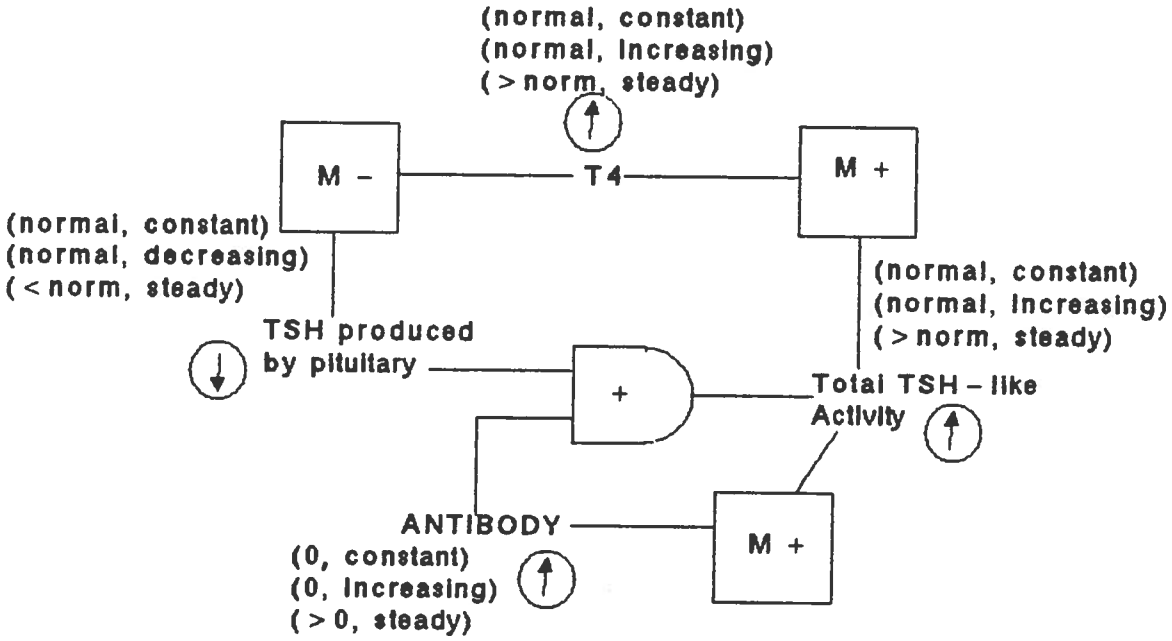

Figure 8-1. Directions of change in the simulation of Graves disease. M- is a monotonic decreasing function. M+ is a monotonic increasing function. The third constraint is an addition constraint.

Our simulation model follows the prediction, propagation and constraint rules described by Kuipers (1986, Appendices A, B, C and D) At the start of the simulation, the net is initialized (Table 8-1). All parameter objects except the antibody object, which is initialized to zero and increasing, are set to normal (no IQ value). The IQ values are propagated to finish the first qualitative state. Prediction rules are applied to set the next ordinal value for each parameter. Prediction rule P2 is applied, since all parameter objects are moving towards a landmark value and they are connected by monotonic functions. The IQ values are set to steady and the simulation is finished. Table 8-1 shows each of the qualitative time states. The values are perturbed in the correct direction as can be seen by their IQ values. Thyroid hormone is now elevated and the TSH produced by the pituitary is suppressed to below normal, as is the case in Graves disease.

Table 8-1. Simulation of Graves Disease. Time values are normal (no antibody present) T-1 and T-2

Quantity	(N)	(1)	(2)
Antibody	(zero const)	(Ø inc)	(>Ø std)
total TSH like activity	(norm const)	(norm inc)	(>N std)
T4	(norm const)	(norm inc)	(>N std)
TSH produced by pituitary	(norm const)	(norm dec)	(<N std)

At the beginning of the simulation, all values are normal and constant (see Table 8-1). In qualitative state T1,

antibody levels begin to increase. The total TSH like activity in the serum begins to increase at the same time antibody levels are rising. Increase in the TSH activity causes the T4 levels to increase. Increased negative feedback on the pituitary by the rising levels of T4, begins to decrease the levels of TSH produced by the pituitary. In qualitative state T-2, levels of T4 are greater than normal, as are the levels of TSH like activity and antibody. The TSH produced by the pituitary is now less than normal. All the parameters are steady and the simulation is now finished.

9.Ø Conclusion:

We have created a knowledge structure which is capable of qualitatively simulating some disease processes of the thyroid. The model is multileveled and corresponds to the different conceptual point of views or "mini-models" an expert might use. This is grounded in the empirical findings of the domain literature. This model is different from other multileveled representations in that its structure is derived from studies of expert explanations and the resulting representation is in principle designed

around this organization.

The resulting physiological model should provide a more satisfying interface with users since it corresponds more naturally with their own conceptual models. As has been suggested earlier, this parceling of information into smaller packages is consistent with what is known about the limits of human information processing. the incorporation of these physiological and pathophysiological representations into expert systems will allow them to produce coherent explanations which underly program produced conclusions and in response to user questions.

Further research is needed to find the best integration of these models into a rule-based system. One possible method, would be to have the rule-based system perform the problem solving and diagnosis, and have the causal simulation model provide the explanations. The potential for this approach is very promising. Additional empirical studies of experts with more rigorous transcript analysis are also warranted to refine the existing knowledge structure and as a check for consistency across experts.

APPENDIX A

Verbatim Transcript

(This transcript used for generating Figure 6-5)

****
(Q1) What is the etiology and pathogenesis of Hashimoto's disease?
****

1 It's precise etiology is unkown
2 some people feel there is initially
3 some insult to the thyroid gland
4 which causes formation of thyroid antibodies
5 that continue to attack the gland
6 and contribute to its ultimate destruction
7
8 some people feel that it may be viral
9 as in Subacute thyroiditis
11 there seems to be a familial incidence
12 and a underlying genetic predisposition
13 ahhh.. in the development of Hashimoto's
14 so it may be a combination of factors
15 but the precise cause is unknown
("what's the other part of the question? A: pathogenesis)
16 Pathogenesis is believed to be the the
17 constant inflamatory reaction
18 relative to the antibody reaction
19 with components of the thyroid cells
20 to which they....
21 to which ...have been formed
22 which are the antigenic components
23 and resulting inflammation
24 results in the destruction of the thyroid gland.
25
26 the thyroid inflammatory reaction
27 is piecemeal rather than diffuse
28 resulting in some degree of nodularity
29 and the increased TSH production
30 usually results in some enlargement of the gland
****
(Q2: What is the etiology and pathogenesis of dyshormongenetic goiter?(DHG))
****
31 DHG is due to a...
32 inherited enzyme defect
33 in the thyroid
34 in one of the steps of thyroid production

35 and its very often partial
36 and it may be complete in which case
37 the patient is very hypothyroid
38 from childhood on, if it's complete
39
40 in most cases it is complete
41 and the increased TSH production
42 may increase...
43 overcome the block...
44 it doesn't overcome the block
45 but enough thyroid hormone is produced
46 to keep the patient euthyroid for some period of time
47 until some other factor
48 results in further interference..aggravation...accentuation
49 of the enzyme defect
50
51 and then the patient may become clinically hypothyroid

****

(Q3: HOW DOES THE ETIOLOGY OF HASHIMOTO'S LEAD TO A DECREASED T4?)

****

52 well the etiology itself doesn't
53 it's the pathogenesis that causes destruction of the gland
54 so the gland...is less..
55 less actual gland to produce normal thyroid hormone

****

(Q4: HOW DOES IT CAUSE INCREASED TSH?)

****

56 by resulting in lowering of the thyroxine level
57 secondary elevation from the pituitary
58 due to a loss of the negative feedback inhibition
59 of TSH production

****

(Q5: AND HOW DOES THE LOWERING OF THE T4 CAUSE A INCREASED TSH?
HOW DOES IT CAUSE A LOSS IN NEGATIVE FEEDBACK?)

****

60 Well, because the normal feedback mechanism...
61 ..when the T4 gets to a certain degree level
62 it slows down the production of TSH
63 by the pituitary
64
65 and in the absence of adequate amounts of T4
66 TSH production increases
67 because the break of T4 is the one that does it.

****

(Q6: How does the pituitary sense the levels of T4?)

****

68 Oh, I am not sure of the actual mechanism
69 I think there's been a lot of work done it recently..
70 which I am not up to date reading on but...
71 T4 receptors on TSH producing cells
72 in the pituitary
73 .....there may T3 receptors too
74 I think there are some work which suggests that
75 it's actually the process of deidonation to T4 to T3
76 which actually affects TSH production
77
78 I am not sure that has been proven correct

****

He now interprets lab data:

The T4 (some confusion over the strange units CPB) ..it's low
T3 level resin uptake is low
FTI is low
T3 is midnormal range
TSH is elevated
and the radioactive iodine uptake is elevated

---

79 well the fact the RAIU is elevated
80 inspite of hypothyroidism with elevated TSH
81 kind of shunts me over into the possibility of DHG
82
83 Ok I'd put the patient on thyroxine therapy
84 and that should suppress the TSH down to extremely low levels
85 and suppress the RAIU

****

(Q7: WHY IS THERE A LARGER PBI TO T4 DIFFERENCE?)

****

86 the reason for that..
87 there is one form of DHG
88 where they make iodinated proteins
89 which are measured as pbi
90 but they are not measured as T4 by the modern techniques
91
92 So this discrepancy between the two
93 would be in favor of DHG
94 and we see after she got the perchlorate
95 70% of the thyroid was reduced
96
97 so she has a thyroidal peroxidase deficiency

****

Q8: WHY IS THE RAIU ELEVATED?)

****

98 because the thyroid is being stimulated

99 by large amounts of TSH
100 the thyroid gland itself
101 basically can't function normally
102 I mean it can respond to TSH
103 and trap iodine
104 but it can't make it into hormone
****
(Q9: WHAT ACCOUNTS FOR THE RAPID IODINE TURNOVER?
****
105 the absence of the peroxidase
106 means the iodine can be trapped
107 but not oxidized and organified
108
109 so any of the iodide in the gland
110 that is not incorporated into an organic molecule
111 will be released by perchlorate
****
END

APPENDIX B
Verbatim Transcript of Expert Protocol
(This transcript used for generating Figure 6-6)

****

(Q1)What causes the increased T4 in Graves disease?

****

1 increased production and release of the thyroid hormone

****

(Q2) What is the initial insult?

****

2 production of thyroid immunoglobulin stimulati hormone,
3 which has a TSH like activity on the thyroid cells

****

(Q3)How does that activity translate into increased T4 production?

****

4 well, it acts like TSH
5 in increasing all the steps of
6 trapping and synthesis and release of the hormone.

****

(Q4)In this case how do you explain the simultaneous development of elevated serum T3, low serum T4 and elevated TSH?

****

7 Well, it's kind of hard, as a matter of fact.
8 I could presume
9 if the patient was in fact becoming hypothyroid
10 either because of the antithyroid drug
11 or possibly just spontaneously.
12 Why she would have an elevate T3 by RIA
13 at this point is difficult to access.
14 other than that she might be having a reversible...
15 what we call a reverse T3
16 or euthyroid sick syndrome
17 where she is converting more of her T4 into T3
18 But the pituitary being more sensitive to T3,
19 I think would be turned off.
20 -would not be putting out an elevated TSH
21 So I have trouble putting those two things together.
22 presumably she had a suppressed TSH
23 when she was first diagnosed nine months ago.
24 If the TSH had not been measured at that time
25 though what we see is a mild elevation
26 I don't know what kind of number you are talking about
27 because if you are talking about a number like 7,8 or9
28 which would be a mild elevation
29 sometimes we see that in postmenopausal women for

instance.
Sometimes we see it in patients with prolactinomas and so forth
But those are outside possibilities
you have to think about in unusual situations
when you see elevated TSH you don't expect
I don't know if there is any other way to explain this
divergence between the T4 and the elevated T3
unless originally she had a much more significantly
elevated T3
and she had in fact a form of T3 toxicosis
maybe where T4 may have been elevated but just mildly
T3 would have been much more radically elevated
and so what we are seeing now is
what appears to be disproportional
even though both may have fallen

****

(Q5) Just on the basis that the dye blocks conversion of T4 to T3 in all tissues, what do you expect the lab tests to be for T4,T3 and TSH?

****

I expect to see T4 to be high-normal
I expect to see the T3 to be low-normal or low
and the TSH very slightly elevated

****

(Q6)How do you explain these values?

****

Well, just by virtue of what you say
conversion of T4 to T3 is inhibited
by the large amount of iodide in this drug
and by the compund itself.
The normal conversion of T4 to T3 would be inhibited
and so the T4 level would tend l
to stay in the upper normal range...
It probably wouldn't go above normal
It might go right at the edge of normal.
T3 of course would be deressed
because of the conversion T4 to T3 is inhibited
the pituitary being much more sensitive
to the T3 level
both in the serum
and possibly due to interpituitary conversion...
TSH might go up

****

case presented fig 2/(reading problem while interpreting)

****

hyperthyroidism seven year old girl
very unusual age for hyperthyrodism
or Grave's disease
she did have an enlarged thyroid

67 elevated T4 level
68 normal TBG
69 so there wasn't a falsely elevated T4 level
70 So she appears to be hyperthyroid
71 both clinically and on multiple confirmatory levels
72 And she started on antithyroid medication
73 was stopped because of an adverse reaction.
74 Is interesting to note but not essential.
75 TSH was inappropratiely elevated
76 when she was thyrotoxic
77 and this brings to mind the possibility
78 that she has infact a TSH producing adenoma of the pituitary
79 Which would be the main cause for such an incorrect (?)
80 inappropriately raised TSH.
81 Subtotal thyroidectomy was performed.
82 Postoperatively she became hypothyroid
83 then became thyrotoxic again
84 she was agian controlled..
85 then it recurred with inappropriate elevated TSH levels.(?)
86 with a good but inappropriate response to TRH.
87 I don't know what a good but inappropriate response,..
88 I am not sure what an good response is [2-3 or 6-8,9 ??]

(reads last sentence verbatim: Administration of large amounts of T3 or T4 reduced the response of large doses to TRH, but not to the degree observed in normal subjects.)

89 there is a condition, called pituitary insensitivity
90 and I think this is what they do.
91 they respond to large amounts of T3(????)
92 So I assume this is what she has,
93 this pituitary insensitivity to normal T3 levels.

****

(Q7) So how does this insensitivity cause you to be thyrotoxic?

****

94 Because the pituitary not sensing normal T3 level
95 puts out more TSH
96 which stimulates the thyroid
97 much the same way TSIG does.
98 there's just topo much TSH produced
99 because the pituitary is not told to shut off
100 at the normal level of T3.
101 It doesn't shut off until the
102 T3 level gets excessively high.

****

(Q8)How does the TRH stimualtion test results confirm your conclusion?

****

It shows the pituitary
is producing TSH
and that it has a of TSh available to release.
If it were a TSh producing tumor of the pituitary
-usually they don't respond
or they respond very little.
they're already putting out maximal amounts of TSH.
So that [articular bit of information would make it less
likely she had a pituitary tumor.

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